the melanocytic stem cell population and replace it with a pool of aggressive, invasive cells. The new developmental work directly feeds to the deeper understanding of the origins of melanomas.

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How to Shape Cells and Influence Polarized Protein Trafficking

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Posttranslational modifications of tubulin likely generate the functional diversity of microtubules. In this issue of *Developmental Cell*, Loktev and colleagues (2008) describe a novel protein BBIP10 with dual roles: it is required for ciliogenesis as well as acetylation and stabilization of microtubules.

Microtubules (MTs) are dynamic structures consisting of hollow cylinders about 25 nm in diameter, comprised of 13 protofilament polymers of α- and β-tubulin. They depend on GTP for polymerization and are polarized structures. The microtubules play key roles in, for example, the intracellular transport of vesicles and mitochondria and formation of the mitotic spindle. They also form the main structural components of the ciliary/flagellar axoneme in a typical cart-wheel arrangement of nine outer microtubular doublets either lacking ("9+0", as in most nonmotile cilia) or containing ("9+2", in motile cilia) a central pair. MTs are also found in the two centrioles embedded within the centrosome, which serves as an important MT organizing center for the cell. One of these centrioles is given over to form the basal body at the cilia base.

Not all microtubules are equal, and subpopulations are established by a series of posttranslational modifications including tyrosination/detyrosination, polyglutamylation, polyglycylation, phosphorylation, palmitoylation, and acetylation. Most of these modifications accumulate on the outer surface of stable MTs, permitting interactions with MT-associated proteins, molecular motors, or plus-end tracking proteins. This combination of modifications drives tubulin diversity and may relate to cell type-specific and organelle-confined functions. Although the structure and, to some extent, the function of these cytoskeletal filaments have been scrutinized, the mechanism of their modification and their specific subcellular roles is less well defined.

Our understanding of some of these microtubular properties has advanced with the publication of the study of Loktev et al. (2008) in this issue of *Developmental Cell*. The group reports the identification of a protein (BBIP10) that interacts directly with components of the BBS protein complex (BBSome), which is important for ciliogenesis. In vitro, BBIP10 colocalized with BBS4 in primary cilia but not the centriolar satellites, suggesting a direct role in cilia function. Indeed, knockdown of BBIP10 reduced BBSome assembly and ciliation both in vitro and in vivo. Depletion or mutation of individual BBS proteins can give rise to the multiple congenital anomaly syndrome Bardet-Biedl, a defining ciliopathy. Could *BBIP10* therefore be a missing BBS gene? The team did not detect mutations in over 300 BBS patients without prior mutations in any of the BBS genes (*BBS1-12*). Since BBIP10 function is not limited to the BBSome (see below), it is possible that most human *BBIP10* phenotypes are lethal during embryonic stages and thus remain essentially undetectable. Given the complex partnership of BBS proteins, their collective importance for cilia maintenance and function, and the oligenic nature of *BBS* mutant alleles, it would not be surprising if sequence variants had modifier effects on ciliary function. Hypomorphic mutations in BBIP10 may give rise to an as yet unidentified human phenotype.

BBS proteins have been implicated in the modulation of microtubular transport (e.g., BBS4 is an adaptor protein involved in retrograde MT transport [Kim et al., 2004], centrosome function, and cell

migration [Tobin et al., 2008]). Depletion of BBIP10 results in loss of the ability of BBS4 to associate with its complex partners, indicating its importance for incorporation of BBS4. This is likely to be a microtubule-independent role. But what is the mechanism by which BBIP10 functions? The clue came from the careful observation that BBIP10 knockdown culminates in decreased MT acetylation. In addition, the density of cytoplasmic MTs was diminished, but the levels of unpolymerized α-tubulin were increased, suggesting BBIP10 is required for stabilization of MTs. Both MT stabilization and acetylation were shown to be independent of each other and of BBS proteins individually or functioning as a complex. BBIP10 overexpression assays confirm its role in MT acetylation, but the exact mechanism remains to be defined. Importantly, the loss of BBIP10 does not affect either tyrosination or glutamylation of MTs.

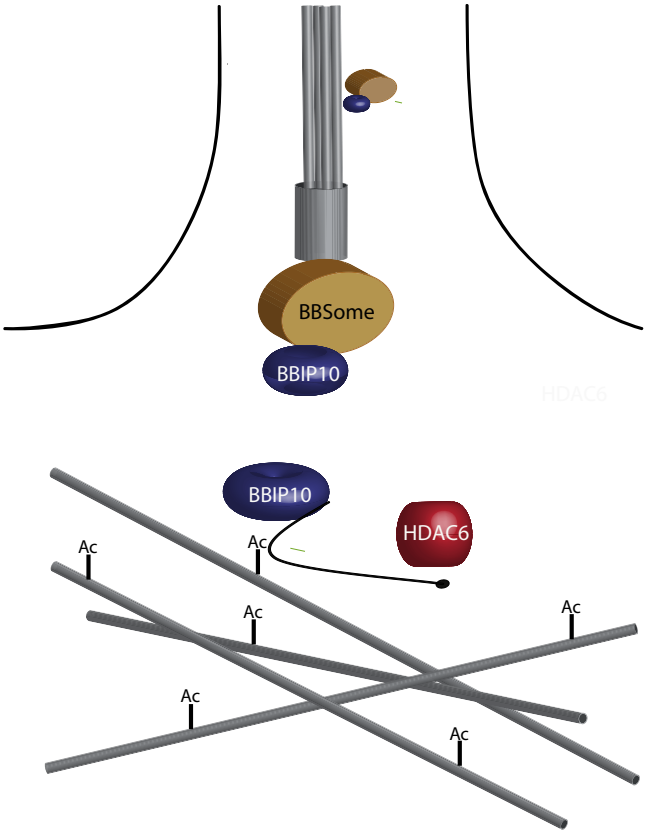

Figure 1. Proposed Function of BBIP10
BBIP10 is important for the formation of the BBSome and for acetylation and stabilization of microtubules. Ac, acetylated Lys40.

MT acetylation occurs on lysine 40 of α-tubulin, thought to reside on the luminal surface of MTs (Hammond et al., 2008) and is thought to promote kinesin-1 binding (Reed et al., 2006). Acetylation is commonly found on stable MTs and is widespread among several cell types, but the responsible acetylases have yet to be identified. Nonetheless, two deacetylases, HDAC6 and Sirt2, have been discovered and knockdown of either results in hyperacetylation of α-tubulins (Hubbert et al., 2002; Matsuyama et al., 2002; North et al., 2003). Loktev et al. (2008) found that pharmaceutical inhibition of HDAC6 partially rescued tubulin acetylation and, furthermore, that BBIP10 directly interacts with HDAC6, thus providing a glimpse of the possible mechanism by which BBIP10 influences acetylation.

There appear to be two distinct pools of BBIP10, one associated with the BBSome in the cilium and the second diffusely distributed throughout the cytoplasm. These researchers demonstrate clearly that depolymerization of MTs has no impact on formation of the BBSome. BBIP10, therefore, appears to have two separate functions: first, the maintenance of the BBSome with consequent formation of cilia, and second, presumably through the action of the cytoplasmic fraction, the stabilization and acetyl modification of MTs (Figure 1). Although acetylation, per se, is not essential for survival or ciliation (at least not in *Chlamydomonas* [Kozminski et al., 1993] and *Tetrahymena* [Gaertig et al., 1995]), perhaps one function of BBIP10 is to coordinate polarized protein trafficking and cilia formation. The reasons for this are unknown but may relate to microtubule-based (e.g., intraflagellar transport) signaling. Although MT destabilization is likely to impact on early development, the generation of hypomorphic mutant models should illuminate further the role of BBIP10.

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